FEATURE REVIEW

Personalized Medicine and the Practice of Medicine in the 21st Century

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> "If it were not for the great variability among individuals, medicine might as well be a science, not an art." Sir William Osler, 1892

The renowned Canadian physician and McGill alumnus got it right. Much of medical science over the past century has documented intra-and inter-individual variability, however the rationale for this variability is not well understood and not often applied in clinical practice. Indeed most therapeutic strategies rely on data derived from randomized clinical trials (RCTs) and large observational studies, and applied to the so-called "statistically average" patient. Although medicine will continue to remain very much an art, just over a hundred years after Osler's observation, we are beginning to understand the factors driving inter-individual variability. Armed with details of individual variation, physicians could divide patients into subgroups and predict which are likely to have an aggressive or indolent form of a disease and which would respond to one drug rather than another.

The emergence and continued growth of personalized medicine will catalyze fundamental changes at many different levels in the future of health care and health systems. The objective of this special focus article is to describe the role and increasing importance of personalized medicine in health care, as well as discuss some of the ongoing challenges for integrating personalized medicine into contemporary medicine.

WHAT IS PERSONALIZED MEDICINE?

A personalized medicine approach to providing health services involves integrating genomics technologies and advances with clinical and family histories in order to more coherently tailor therapeutics to individual patients. A key component of personalized medicine is translating the science of pharmacogenomics into clinical practice. Pharmacogenomics is increasingly seen as holding the potential for tailoring prescriptions to defined sub-populations and possibly individuals, based upon genetic make-up, and therefore, ultimately improving the effectiveness and safety of drugs.

A BRIEF HISTORICAL OVERVIEW OF PHARMACOGENETICS AND PHARMACOGENOMICS

The capacity for genetic differences to affect response to the biochemical environment has been known for over 100 years. Historically, one of the first indications of genetic polymorphism in drug metabolism was suggested by studies on alkaptonuria in 1902 (1). Alkaptonuria is a disorder in which the enzyme homogentisate oxidase does not correctly process its intended target substrate, homogentisic acid, leading to a build up of that substrate. Alkaptonuria is usually asymptomatic, but can lead to arthritis.

A curious observation of hemolysis among African-American soldiers in response to taking the antimalarial drug primaquine provided evidence of genetic variation in response to drug ingestion when further studies demonstrated that this primaquine - induced hemolysis was due to a genetic deficiency of the enzyme glucose -6-phosphate dehydrogenase (G-6-PD) (2). The significance of pharmacogenetics to the clinical care of patients was shown by Kalow and Gunn who observed an excessive neuromuscular blockade and longer-lasting apnea in some patients who had been administered the neuromuscular blocking agent, succinylcholine, as part of undergoing electroconvulsive therapy (3). These and other observations established the early foundation of the

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field of pharmacogenetics.

The more recently coined term, "pharmacogenomics" is more encompassing describing the impact of genomic information on the drug discovery process. Therefore, pharmacogenomics includes identifying candidate genes and polymorphisms, correlation of polymorphisms with therapies, prediction of drug response and clinical outcomes, reduction in adverse events, and selection and dosing of drugs based on genotype (4). Thus, the prediction of polymorphisms has implications for reducing adverse events, improving the design of rational drug development, and eventual drug prescription.

Some of the anticipated long-term benefits of pharmacogenomics include the potential for "personalized" or "customized" prescriptions, improved patient compliance, reduction or elimination of certain adverse events and the reduction in cost of disease management. The potential applications for genotyping for pharmacogenomics purposes are diverse and are primarily driven by three requirements (4-7): first, the need to determine the safety and efficacy of an experimental new drug prior to approval; second, the need to establish an individual's genetic predisposition to a disease state; and, third, the need to protect patients against possible adverse drug reactions by identifying poor metabolizers at the initiation of drug therapy. The use of genotyping in the identification of poor metabolizers prior to the initiation of drug therapy is an appealing emerging opportunity for pharmacogenomics. Physicians may choose to screen their patients before administering certain drugs.

PERSONALIZED MEDICINE AND DRUG DEVELOPMENT

The basic science of pharmacogenomics is already contributing substantially to drug research and development (R&D). The pharmaceutical industry has embraced pharmacogenomics and the use of pharmacogenomic strategies has become an integral component to well over 100 clinical trials. Indeed, a recent count of the trials employing pharmacogenomic strategies yielded 144 trials that are currently recruiting and an additional 97 that are completed (8).

The drug discovery process has generally been labour-and-time-intensive, with industry scientists selecting new molecular entities (NMEs) that correlate with appropriate targets and testing them through preclinical and clinical phases to validate safety and efficacy of the more promising candidates. However, knowledge garnered from the Human Genome Project coupled with a novel complement of genomic technologies provides researchers with a much broader range of targets at which to aim potential therapeutic interventions. The wide array of genomic technologies including high-throughput technologies, global gene expression analysis, genome-wide functional analyses and gene expression monitoring allows for the genetic analyses of numerous NMEs for toxicity and efficacy, thus streamlining the drug discovery process while enhancing prospects for better therapies (4).

The identification and screening of candidate genes, polymorphisms, correlation of polymorphisms with possible therapeutic targets, prediction of drug response and clinical outcomes, and selection of therapeutic dosages on the basis of genotype, are all activities that fall in the purview of pharmacogenomics (4). Thus, the field of pharmacogenomics can impact the drug development process throughout all stages of the R& D pipeline.

THE PROMISE AND POWER OF PERSONALIZED MEDICINE

There are several well-known examples of personalized medicine applications based upon using pharmacogenomics (table 1). However, clinical applications of personalized genomic medicine are occurring at a variable pace, and the following examples will serve to highlight some of the reasons for this inconsistency in application.

Table 1. Some Current Pharmocogenomic Examples

Drug	Polymorphic gene
Warfarin Phenytoin Tolbutamide, glipizide	CYP2C9
Flouxetine Codeine	CYP2D6
5-Flourouracil	Dihydropyrimidine dehydrogenase
Antiepileptic drugs	MDR1 (or ABCB1)
6-Mercaptopurine 6-thioguanine Azathioprine	TPMT
β-agonists (e.g. albuterol)	β_2−adrenergic receptors
β-blockers (e.g. propranolol)	Angiotensin-converting enzyme (ACE)
Losartan	Angiotensin II type I-receptor (AT-1)
Irinotecan	UDP-glucoronosyltransferase 1A1 (UGT1A1)
Abacavir	Human leukocyte antigen (HLA)
Sulfonamides Isoniazid, Procainamide Hydralazine	N-acetyltransferases (NATs)
Imatinib mesylate (Gleevec)	BCR/ABL
Herceptin (transtuzumab)	Her-2/neu
Thioridazine	CYP 2D6
Strattera (atomoxetine)	CYP 2D6

Herceptin® and HER-2/neu Testing

The breast cancer chemotherapeutic trastuzumab (Herceptin®) is often seen as the "poster child" for

personalized medicine. Indeed, the story of the development and approval of Herceptin® represents an interesting case study of personalized medicine.

Herceptin® is a genetically engineered humanized monoclonal antibody that was developed after the discovery of the human epidermal growth factor receptor-2 protein (HER-2/neu). The discovery that the human epidermal growth factor receptor-2 (HER-2) protein on the surface of breast cancer cells is over expressed in approximately 25-30% of breast cancer patients led to the development of a therapeutic antibody that could target HER-2 (9,10). Trastuzumab was approved by the Food and Drug Administration (FDA) in 1998 (11). Trastuzumab was initially approved in combination with paclitaxel for patients with metastatic breast cancer whose tumors over-expressed HER-2 and who had not received any treatment for their disease. Trastuzumab, as a single agent, is indicated for patients with metastatic breast cancer whose tumors over-expressed HER-2 and who had not responded to other chemotherapeutics.

The story of HER-2 testing and Herceptin® illustrate a fast and successful adoption of a pharmacogenomic intervention. In its first full year on the U.S. market, Herceptin's® sales were $188 million (12). Since that time, the sales of Herceptin® have continued to grow rapidly. Herceptin® is among the top 20 best-selling biotech drugs, with sales of $747 Million in 2005 and a growth rate of 56% between 2004 and 2005 (13).

Other oncologic drugs that appear to have followed a similar path through the pipeline and may be considered examples of personalized medicine include imatinib mesylate (Gleevac®) and rituximab (Rituxan®). In patients with Philadelphia chromosome positive chronic myeloid leukemia (CML), Gleevac® is a protein tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase (14,15). Rituxan® is indicated for CD20-positive, B-cell non-Hodgkin's lymphoma (16,17).

Genotyping for Warfarin Dosing

More recently, a "real world" application of personalized medicine has been described that involves the stratification of the commonly prescribed anticoagulant warfarin dosing based on variation in the vitamin K epoxide reductase complex 1 (VKORC1) and cytochrome P450 2C9 (CYP450 2C9) gene polymorphisms (18-20). Indeed, the U.S. FDA Clinical Pharmacology Sub-Committee (CPSC) Advisory Committee voted to re-label the dosing of warfarin to take into consideration the new information (21).

Tests for CYP450 drug metabolizing enzymes

A major cause of variability in drug response is due to mutations in cytochrome P450 (CYP450) drug metabolizing enzymes (22). These mutations are relevant to many commonly used drugs such as anti-depressants and cardiovascular drugs, and the most-studied enzyme, CYP2D6, is estimated to be a major contributor to the metabolism of 25% of drugs (23).

The visibility of CYP450 testing was raised substantially with the FDA approval of the AmpliChip® CYP450 test, developed by Roche Molecular Diagnostics, Inc. Its approval has been called a "milestone" in personalized medicine (24). The AmpliChip® tests for genetic mutations in two common drug metabolizing enzymes (CYP2D6 and CYP2C19) that are relevant to many drugs, and thus the test has received widespread attention in both the industry and lay press.

Despite widespread interest in the use of AmpliChip® and similar CYP450 tests, adoption into clinical practice has been slow. A major challenge to the adoption of CYP450 tests is the current lack of evidence about their clinical utility and how to use the tests in clinical practice. It has been difficult to determine when testing would be useful for many reasons, including the multi-factorial nature of drug response, lack of evidence linking mutations to important clinical outcomes, and variability not only across but also within drug classes (25). Furthermore, since a single CYP450 mutation is unlikely to be responsible for drug response, tests such as AmpliChip® are not gatekeeper tests that determine the use or non-use of a drug, such as HER2 testing for Herceptin®.

PARADIGM CHANGES IN HEALTH CARE AND HEALTH CARE SYSTEMS

The examples of current applications described above illustrate the potential for pharmacogenomic strategies to improve health care by risk-stratification and more tailored therapeutic interventions. But they also portend significant challenges to our health systems, and highlight the need for significant changes including infrastructure changes in health care.

High-Quality, Unified Systematic Databases Are Essential

The need to match patient genotypes to drug responsiveness is inherently a complex endeavour and no clinician can reasonably be expected to achieve this unaided. This problem underscores the critical lack of the use of appropriate, efficient and effective information technology (IT) in health care delivery (26, 27). Thus, one key paradigmatic change that personalized medicine will bring to the health care infrastructure is the need to advance existing IT technologies and develop high quality databases. However, linking clinical data and genomic data sets is likely to present a formidable integration challenge. An

even greater barrier will be the incorporation of treatment algorithms informed by these data.

Post-marketing Surveillance

Adverse drug reactions (ADRs) constitute a major worldwide problem. The promise that the use of pharmacogenomic strategies might overcome the serious public health problem of ADRs is one goal of current research efforts. Pharmacogenomics appears promising as an approach to drug surveillance in the post-approval period. However, there remain considerable technical and regulatory constraints that need to be resolved (28).

Economic and Regulatory Considerations

There are many challenges to determining the value of pharmacogenomic interventions. Many of these challenges are technical issues, such as a lack of data that links interventions to health outcomes and costs, and that provides comparisons to alternative approaches. Another technical challenge is the need to evaluate multi-factorial conditions and diagnostic-drug combinations to assess value. Other challenges emerge from the policy context. The value of diagnostics is often harder to measure than the value of drug therapies. For example, payers may be concerned that the up-front costs of testing will be higher than the downstream savings.

Although numerous observers have discussed the potential value of personalized medicine and pharmacogenomics, there is currently little empirical evidence supporting such claims. To date, there are few cost-effectiveness analyses of pharmacogenomic interventions, with inconclusive results as to whether such interventions are a relatively good value (29). There are also relatively few mechanisms or incentives to assess economic value from a societal perspective. Coverage and reimbursement policies may be considered the ultimate incentive for industry to bring products to the market. However, there is currently much ambiguity about whether pharmacogenomic interventions are or will be covered, by whom, and at what rates.

Table 2. Some Ethical and Policy Issues Relevant to Personalized Medicine

Fairness in access to genomic technologies
Intellectual property
Regulatory oversight
Reimbursement/Health care insurance
Patient education
Provider education
Healthcare system infrastructure
R&D incentives for industry
What to do if no alternatives are available
Consequences of not performing a test if available
Privacy and confidentiality of information
Fairness in the use of genomic information by insurers, employers, courts, schools, adoption agencies, and the military, etc.
Psychological impact, stigmatization due to misunderstanding about pharmacogenomics information.
Uncertainties and misunderstanding regarding gene tests

Ethical Challenges

There are also security, ethical and privacy issues to be resolved (4, 30). Some of these are highlighted in table 2.

SUMMARY AND CONCLUSIONS

In this special focus article, I have highlighted some of the key considerations for better integrating personalized medicine into clinical practice.

Using pharmacogenomic strategies in conjunction with family and clinical histories offers exciting and promising advances towards personalized medicine and novel tools to add to the repertoire of clinicians. However, a number of challenges remain towards fully realizing the potential of these genomic technologies and strategies. These challenges will affect the delivery of health care and health systems at multiple levels including infrastructure changes, development and implementation of high quality databases and IT-based technologies, education of current and future healthcare professionals, and appropriately resolving ethical and policy societal concerns. Indeed, it is essential that ethics and policy develop in tandem with scientific advances in pharmacogenomics. To do so, pharmaceutical and biotech companies, diagnostic companies, researchers, medical educators, information technology managers, healthcare providers, laboratories, patient advocates, policy makers and other stakeholders must all work together to carefully review the issues at hand and consider their interconnected implications.

My charge to the current medical students and residents who will become the future health care leaders of tomorrow is to become trailblazers by actively participating in directing research priorities at all phases of discovery and diffusion, and anticipating what will be the challenges and opportunities for genomics research and personalized medicine in order to promote public health and the common good.

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About the Program in Personalized Medicine and Targeted Therapeutics

The mission of the Program in Personalized Medicine and Targeted Therapeutics is to advance knowledge of and promote informed decision-making about the effectiveness of pharmaceutical products, services, and policies, with a particular focus on personalized medicine technologies. The program accomplishes its mission through state-of-the-art research, training programs, consultation to government agencies on public policy initiatives, and national and international collaborations.